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(54) **Cardiotonic aroylthiazolones.**

(57) Aroylthiazolones enhance myocardial contractile force and are useful as cardiotonics in the treatment of heart failure.

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CARDIOTONIC AROYLTHIAZOLONES

BACKGROUND OF THE INVENTION

This invention relates to the certain aroylthiazolones which enhance myocardial contractile force and are useful as cardiotonics in the treatment of heart failure.

Heart failure is that physiological condition resulting from the inability of the ventricular myocardium to maintain adequate blood flow to the peripheral body tissues and includes congestive heart failure, backward and forward heart failure, right ventricular and left ventricular heart failure, and high-output and low-output heart failure. Heart failure can be caused by myocardial ischemia, myocardial infarction, excessive alcohol usage, pulmonary embolism, infection, anemia, arrhythmias and systemic hypertension. Symptoms include tachycardia, fatigue with exertion, hyspnea, orthopnea and pulmonary edema.

Treatment involves either removal or correction of the underlying cause or involves control of the heart failure state. Management or control can be accomplished by increasing cardiac output or by decreasing cardiac workload. While workload can be reduced by reduction of physical activities and physical and emotional rest, increasing cardiac output has traditionally involved digitalis therapy. Digitalis stimulates contractile force of the heart which

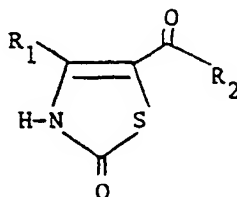
increases cardiac output and improves ventricular emptying. In this way digitalis therapy normalizes venous pressure and reduces peripheral vasoconstriction, circulatory congestion, and organ hypoperfusion.

Unfortunately, optimal doses of digitalis vary with the patient's age, size and condition and the therapeutic-to-toxic ratio is quite narrow. In most patients the lethal dose is only about five to ten times the minimal effective dose with some toxic effects becoming apparent at only 1.5-2 times the effective dose. For those reasons, dose must be carefully tailored to suit the individual and frequent clinical examinations and electrocardiograms are necessary to detect early signs of digitalis intoxication. Nevertheless digitalis intoxication is reported in up to one-fifth of hospitalized patients undergoing therapy. The need for less toxic cardiotonic agents is thus readily apparent.

Applicants have discovered certain aroylthiazolones which possess potent cardiotonic activity and by comparison to digitalis have fewer toxic effects.

Summary of the Invention

This invention is directed to pharmaceutically active aroylthiazolones of formula 1



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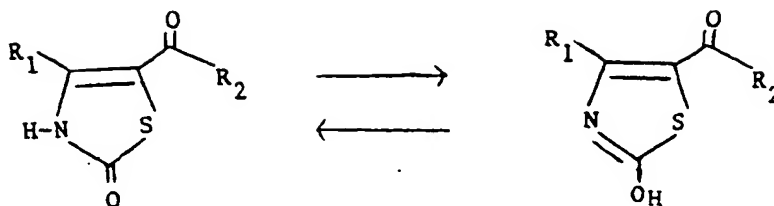
wherein R₁ is a hydrogen or (C₁-C₄) alkyl group; and

R₂ is an unsubstituted benzyl or a phenyl or benzyl substituted with one or two members of the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkoxy, carboxy, carb(C₁-C₄)alkoxy, imidazolyl, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylsulfinyl, trifluoromethyl, cyano, amino, mono and di (C₁-C₄)alkylamino, pyrrolidino, piperidino, morpholino, piperazino, N-(C₁-C₄) alkylpiperazino, and halogen group or a methylenedioxy group.

These compounds enhance myocardial contractile force and are useful as cardiotonics in the treatment of heart failure.

Detailed Description of the Invention

The formula 1 compounds exist in two tautomeric forms structurally depicted in formula 2



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wherein R_1 and R_2 are as defined above. Throughout this disclosure, aroylthiazolones of formula 1 are intended to include the tautomers of formula 2.

The ring nitrogen of the formula 1 compounds can be substituted with a (C_1-C_4) alkyl group, and alkanoyl group such as an acetyl group, or a benzoyl group. These nitrogen substituted compounds are equivalent to the unsubstituted compounds primarily because the substituted is cleaved upon administration to a patient but also because many of the nitrogen substituted compounds independently possess significant ability to enhance myocardial contractile force and are useful cardiostonic agents.

As used herein the term (C_1-C_4) alkyl and the alkyl portion of the alkoxy, carb (C_1-C_4) alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, mono- and dialkylamino, and N-substituted piperazino groups means a straight or branched alkyl group of from one to four carbon atoms. Illustrative examples of (C_1-C_4) alkyl group are methyl, ethyl, isopropyl, butyl, and *sec*-butyl. The term halogen means a fluoro, chloro, bromo or iodo group.

Preferred compounds of this invention are those compounds of formula 1 wherein R_1 is a hydrogen, methyl, or ethyl group. Also preferred are those formula 1 compounds wherein R_2 is a substituted phenyl group. More preferred are those compounds of formula 1 wherein R_2 is a phenyl

substituted with an amino or a mono- or di- (C_1-C_4) alkylamino group. The most preferred compounds of this invention are those compounds of formula 1 wherein R_2 is a dimethylaminophenyl and those compounds wherein R_1 is methyl.

As examples of compounds of formula 1 there can be mentioned the following:

5-(4-cyanobenzoyl)-4-methyl-2(3H)-thiazolone;

4-methyl-5-(4-fluorobenzoyl)-2(3H)-thiazolone;

5-(3-chlorobenzoyl)-4-isopropyl-2(3H)-thiazolone;

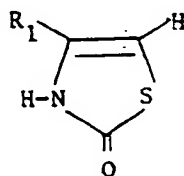
5-(4-dimethylaminobenzoyl)-4-methyl-2(3H)-thiazolone;

4-ethyl-5-phenylacetyl-2(3H)-thiazolone;

5-(3-methoxybenzoyl)-2(3H)-thiazolone;

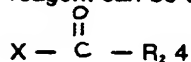
and 5-[(3,4-dimethylthio)benzoyl]-4-propyl-2(3H)-thiazolone.

The formula 1 compounds can be prepared in any manner by standard techniques analogously known by those skilled in the art. For example the formula 1 compounds can be prepared by a Friedel-Crafts acylation of a thiazolone of formula 3



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wherein R_1 is as defined above. The acylating reagent can be an acid halide of formula 4



wherein R_2 is as defined above and X is a bromo group or preferably a chloro group. In addition to the acylating reagent of the Friedel-Crafts reaction can be the free acid or acid anhydride corresponding to the formula 4 acid halide. Mixed acid anhydrides may also be utilized. The Friedel-Crafts reaction is well known by those skilled in the art and has been

reviewed by P.H. Gore in "Friedel-Crafts and Related Reactions", G.A. Olah, editor, Vol. III, Part 1, Interscience Publications, New York, 1964.

The Friedel-Crafts reactions of this invention are performed by premixing about 1 molar equivalent of the appropriate thiazolone of formula 3 with about 1 molar equivalent to about 10 molar equivalents, preferably about 3 molar equivalents, of a Lewis acid catalyst in a suitable solvent, for example, petroleum ethers; a chlorinated aromatic, such as 1,2,4-trichlorobenzene or dichlorobenzene; or a chlorinated hydrocarbon, such as carbon tetrachlo-

ride, ethylene chloride, methylene chloride, chloroform or preferably tetrachloroethane. about 1 molar equivalent to about 10 molar equivalents, preferably about 1.1. molar equivalents, of the appropriate acid halide of formula 4 is added, preferably dropwise, to the mixture of thiazolone, Lewis acid, and solvent and the reaction is allowed to proceed for about 1/2 hour to about 100 hours, preferably from about 1 hour to about 10 hours, depending on the reactants, the solvent, and the temperature which can be from about -78° to about 150°C, preferably about 0° to about 100°C, most preferably about 60°C. The resulting aroylthiazolone may be isolated from the reaction mixture by any suitable art-known procedure, preferably by quenching the reaction mixture with ice water and subsequently removing the product by filtration or extraction and solvent removal or by quenching the cooled reaction mixture with hydrochloric acid and subsequently collecting the solid product by filtration. Purification can be accomplished by, for example, recrystallization, preferably from ethanol.

Lewis acid catalysts suitable for use in the Friedel-Crafts reactions described herein are, for example, a metal, such as aluminum, cerium, copper, iron, molybdenum, tungsten, or zinc; a Bronstead acid, such as a phosphoric acid, sulfuric acid, sulfonic acid, or a hydrohalo acid, such as hydrochloric or hydrobromic acid; halogen substituted acetic acids, such as chloroacetic or trifluoroacetic acids; or a metallic halide, such as a boron halide, zinc chloride, zinc bromide, beryll chloride, copper chloride, iron(III) bromide, iron(III) chloride, mercury(II) chloride, mercury(I) chloride, antimony bromide, antimony chloride, titanium(IV) bromide, titanium(IV) chloride, titanium(III) chloride, aluminum bromide or preferably aluminum chloride.

Alternatively those formula 1 compounds wherein R₂ is a phenyl or benzyl substituted with a C₁-C₄ alkylthio, amino, mono- or di-alkylamino, pyrrolidino, piperidino, morpholino piperazino or N-(C₁-C₄) alkyl-piperazino can be prepared from the corresponding formula 1 compound wherein R₂ is a fluoro substituted phenyl group by an aromatic electrophilic substitution reaction by conventional techniques. Typically the fluoro substituted compound will be allowed to react with an appropriate thiol or amine at elevated temperature.

Further the formula 1 compounds wherein R₂ is a (C₁-C₄) alkylsulfinyl and (C₁-C₄) alkylsulfonyl substituted phenyl and benzyl group can be prepared from the corresponding formula 1 compound wherein R₂ is a (C₁-C₄) alkylthio phenyl or benzyl group by simple selective oxidation. Such oxidations can be performed using hydrogen peroxide or metachloroperbenzoic acid.

The thiazolones of formula 3 are generally available or can be readily prepared by standard laboratory procedures. For example 4-methyl-2-(3H)-thiazolone is prepared by reaction of chloroacetone and potassium thiocyanate in the presence of sodium bicarbonate in aqueous solution by the procedure of Tcherniac, J. Chem. Soc., 115, 1071 (1919).

The acylating agents of formula 4 are simple derivatives of readily available or preparable benzoic acids and phenylacetic acids. Acid chlorides can be easily prepared from the corresponding carboxylic acids by treatment with thionyl chloride by techniques well known to those skilled in the art.

The compounds of formula 1 are cardiotonic agents useful in the treatment of heart failure. These compounds can also be used in any other condition requiring enhanced myocardial contractile force.

The utility of formula 1 compounds as cardiotonics may be determined by administering the test compound (0.1-100 mg/kg) intravenously, intraperitoneally, intraduodenally or intragastrically in a suitable vehicle to a mongrel dog (either sex). The test dogs are anesthetized and prepared by isolating a suitable artery (e.g., femoral or common carotid) and vein (e.g., femoral or external jugular) introducing polyethylene catheters filled with 0.1% Heparin-Na to record arterial blood pressure and administer compounds, respectively. The chest is opened by splitting the sternum at the midline or by an incision at the left fifth intercostal space, and a pericardial cradle is formed to support the heart. A Walton-Brodie strain gage is sutured to the right or left ventricle to monitor myocardial contractile force. An electromagnetic flow probe may be placed around the root of the ascending aorta for measuring cardiac output less coronary blood flow. Heart failure is induced by administering sodium pentobarbital (20 to 40 mg/kg) followed by a continuous infusion of 0.25-2 mg/kg/min. or propranolol hydrochloride (4 mg/kg) followed by a continuous infusion of 0.18 mg/kg/min. to the blood perfusing the heart. Following administration of either of these cardiac depressants, the right atrial pressure dramatically increases and cardiac output is severely depressed. Reversal of these effects by the test compound indicates cardiotonic activity.

The compounds may be administered in various manners to achieve the desired effect. The compounds may be administered alone or in the form of pharmaceutical preparations to the patient being treated either topically, orally or parenterally, that is, intravenously or intramuscularly. The amount of compound administered will vary with the patient, the severity of the cardiac failure and mode of administration.

For topical, oral, or parenteral administration the cardiotionically effective amount of compound and the amount required to enhance myocardial contractile force is from about 0.1 mg/kg of patients body weight per day up to about 400 mg/kg of patient body weight per day and preferably from about 0.3 mg/kg of patient body weight per day up to about 120 mg/kg of patient body weight per day.

For oral administration a unit dosage may contain, for example, from 5 to 700 mg of the active ingredient, preferably about 15 to 235 mg of the active ingredient. For parenteral administration a unit dosage may contain, for example, from 5 to 700 mg of the active ingredient, preferably about 15 to 210. Repetitive daily administration of the compounds may be desired and will vary with the condition of the patient and the mode of administration.

As used herein, the term "patient" is taken to mean warm blooded animals, for example, birds, such as chickens and turkeys, and mammals, such as sheep, horses, bovine cows and bulls, pigs, dogs, cats, rats, mice and primates, including humans.

For oral administration the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions. The solid unit dosage forms can be a capsule which can be of the ordinary gelatin type containing, for example, lubricants and an inert filler, such as lactose, sucrose, or cornstarch. In another embodiment the compounds of general formula 1 can be tableted with conventional tablet bases such as lactose, sucrose or cornstarch in combination with binders, such as acacia, cornstarch or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate.

For parenteral administration the compounds may be administered as injectable dosages of a solution or suspension of the compounds in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water, alcohols, oils and other acceptable organic solvents with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanol and glycols such as propylene glycol or polyethylene glycol, or 2-pyrrolidone are preferred liquid carriers, particularly for injectable solutions.

The compounds can be administered in the form of a depot injection or implant preparation

which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, a silicone rubber manufactured by the Dow-Corning Corporation.

The following specific examples further illustrate the preparation and use of the compounds of formula 1 but are not intended to limit the scope of the invention.

EXAMPLE 1

5-(4-Fluorobenzoyl)-4-Methyl-2(3H)-Thiazolone

4-Fluorobenzoyl chloride (25.3 g, 0.16 mol) was added dropwise to a mixture of aluminum chloride (60 g, 0.45 mol) and 4-methyl-2(3H)-thiazolone - (17.3 g, 0.15 mol) in tetrachloroethane (200 ml). After the addition was complete, the mixture was stirred for 5 hours at 90°C. After the mixture cooled to room temperature, 2N hydrochloric acid (200 ml) was added dropwise. The resulting precipitate was collected, washed with water and then with dichloromethane. The solid was then dissolved in ethanol and heated with charcoal. Subsequent recrystallization from ethanol gave the title compound (18.4 g), m.p. 209-210°C.

In a like manner but substituting o-chlorobenzoyl chloride, m-trifluoromethyl or m,p-methylenedioxyphenylacetyl chloride for p-fluorobenzoyl chloride in the above example gives 5-(2-chlorobenzoyl)-4-methyl-2(3H)-thiazolone, 5-[3-(trifluoromethyl)benzoyl]-4-methyl-2(3H)-thiazolone or 5-(3,4-methylene-dioxyphenylacetyl)-4-methyl-2(3H)-thiazolone, respectively.

In a like manner but substituting 4-ethyl-2(3H)-thiazolone for 4-methyl-2(3H)-thiazolone in the above example gives 4-ethyl-5-(4-fluorobenzoyl)-2(3H)-thiazolone.

EXAMPLE 2

5-[4-(dimethylamino)benzoyl]-4-methyl-2(3H)-thiazolone

Dimethylamine (100 ml of 40% solution) was added to a solution of 5-(4-fluorobenzoyl)-4-methyl-2(3H)-thiazolone. (4.7 g) in ethanol (200 ml). The mixture as stirred in a sealed stainless steel vessel at 102°C for 16 hours. After cooling to ambient temperature the solvent and excess dimethylamine was evaporated. The residue was recrystallized

twice from ethanol to give the title compound mp. 224-228°C.

In a like manner but substituting pyrrolidine, morpholine or 1-methylpiperazine for the dimethylamine in the above example gives

5-[4-(pyrrolidino)benzoyl]-4-methyl-2(3H)-thiazolone.

5-[4-(morpholino)benzoyl]-4-methyl-2(3H)-thiazolones

or 5-[4-(4-methylpiperazino)benzoyl]-4-methyl-2(3H)-thiazolone.

EXAMPLE 3

4-Methyl-5-[4-(Methylthio)benzoyl]-2(3H)-Thiazolone

Gaseous methylmercaptan is added to a solution of 5-(4-fluorobenzoyl)-4-methyl-2(3H)-thiazolone (4.7 g) in ethanol (200 ml) to saturation. The mixture is heated at 120°C in a sealed stainless steel container for 16 hours. After cooling to ambient temperature, the mixture is evaporated to dryness. The residue is recrystallized twice from ethanol to give the title compound.

Substituting 1-butanethiol for methyl mercaptan gives 5-[4-(butylthio)benzoyl]-2(3H)-thiazolone.

EXAMPLE 4

4-Methyl-5-[4-(Methylsulfinyl)benzoyl]-2(3H)-Thiazolone

Hydrogen peroxide (1 equivalent, 30%) is added to a solution of 4-methyl-5-[4-(methylthio)benzoyl]-2(3H)-thiazolone (2.7 g) in glacial acetic acid (80 ml). The mixture is stirred for 3 hours at

50°C. The precipitate obtained on addition of water is recrystallized from ethanol to give the title compound.

Using 2.5 equivalents of hydrogen peroxide and extending the reaction time to 16 hours at 50°C gives 4-methyl-5-[4-(methylsulfonyl)benzoyl]-2(3H)-thiazolone.

EXAMPLE 5

A tablet is prepared from 5-(4-dimethylaminobenzoyl)-4-methyl-2(3H)-thiazolone 250 mg

Starch 40 mg

Talc 10 mg

Magnesium 10 mg

EXAMPLE 6

A capsule is prepared from 4-ethyl-5-phenylacetyl-2(3H)-thiazolone 400 mg

Talc 40 mg

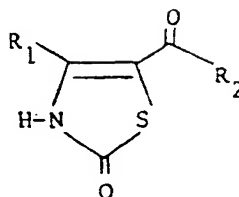
Sodium Carboxymethylcellulose 40 mg

Starch 120 mg

Claims

CLAIMS FOR THE CONTRACTING STATES: BE, CH, DE, FR, GB, IT, LU, NL, SE.

1. A compound of the formula



wherein R₁ is a hydrogen or (C₁-C₄)alkyl group, and

R₂ is an unsubstituted benzyl or a phenyl or benzyl substituted with one or two members of the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkoxy, carboxy, carb(C₁-C₄)alkoxy, imidazolyl, (C₁-C₄)alkylthio, (C₁-

C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, trifluoromethyl, cyano, amino, mono- and di-(C₁-C₄) alkylamino, pyrrolidino, piperidino, morpholino, piperazino, N-(C₁-C₄)alkyl-piperazino and halogen group or a methylenedioxy group.

2. A compound of claim 1 wherein R₁ is a hydrogen, methyl, or ethyl group.

3. A compound of claim 1 wherein R₂ is a substituted phenyl group.

4. A compound of claim 2 wherein R₂ is a substituted phenyl group.

5. A compound of claim 1 or 2 wherein R₂ is a phenyl substituted with an amino or a mono- or di-(C₁-C₄)alkylamino group.

6. A compound of claim 1 wherein R₂ is a dimethylaminophenyl group.

7. A compound of claim 2 wherein R₂ is a dimethylaminophenyl group.

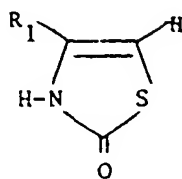
8. A compound of claim 1 wherein R₁ is a methyl group and R₂ is a dimethylaminophenyl group.

9. A pharmaceutical composition comprising a compound of claim 1, 2, 3, 4, 5, 6, 7, or 8 in admixture with a pharmaceutically acceptable carrier.

10. A compound of claim 1, 2, 3, 4, 5, 6, 7, or 8 for use as a medicine.

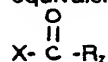
11. Use of a compound of claim 1, 2, 3, 4, 5, 6, 7, or 8 for preparing a medicament for enhancing myocardial contractile force or treating heart failure.

12. A process for preparing a compound of claim 1, 2, 3, 4, 5, 6, 7, or 8 which comprises reacting a thiazolone of the formula



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wherein R₁ is as defined above with 1 to 10 molar equivalents of an acid halide of the formula

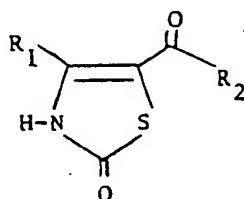


wherein R₂ is as defined above and X is a bromo or chloro group and from 1 to 10 molar equivalents of a Lewis acid catalyst in a suitable solvent at from

0° to 100°C for from 1 to 10 hours and isolating the product.

CLAIMS FOR THE CONTRACTING STATES: AUSTRIA, GREECE, SPAIN.

1. A process for preparing a compound of the formula



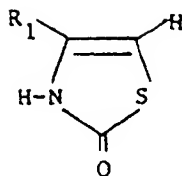
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wherein R₁ is a hydrogen of (C₁-C₄)alkyl group, and

R₂ is an unsubstituted benzyl or a phenyl or benzyl substituted with one or two members of the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkoxy, carboxy, carb(C₁-C₄)alkoxy, imidazolyl, (C₁-C₄)alkylthio, (C₁-

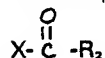
C₄)alkylsulfanyl, (C₁-C₄)alkylsulfonyl, trifluoromethyl, cyano, amino, mono- and di-(C₁-C₄) alkylamino, pyrrolidino, piperidino, morpholino, piperazino, N-(C₁-C₄)alkyl-piperazino and halogen group or a methylenedioxy group, which comprises
a) reacting a thiazolone of formula

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wherein R₁ is defined as above with from 1 to 10 molar equivalents of an acyl halide of the formula



wherein R₂ is as defined above and X is bromo, chloro or a group of formula R₂-CO-O-wherein R₂ is defined as above in the presence of from 10 to 10 molar equivalents of a Lewis catalyst in a suitable solvent at a temperature of from 0° to 100°C,

b) optionally transforming a compound of formula 1 wherein R₂ is (C₁-C₄)alkylthio group into the corresponding derivative wherein R₂ is (C₁-C₄)alkylsulfinyl by selective oxidation, and

c) optionally transforming a compound of formula 1 wherein R₂ is a fluoro substituted phenyl group into the corresponding compounds wherein R₂ is a phenyl or benzyl substituted with a (C₁-C₄)alkylthio, amino, mono-or di-alkylamino, pyrrolidino, piperidino, morpholino, piperazino or N-(C₁-C₄)alkylpiperazino by electrophilic substitution.

2. A process of claim 1 for preparing a compound wherein R₁ is a hydrogen, methyl, or ethyl group.

3. A process of claim 1 for preparing a compound wherein R₂ is a substituted phenyl group.

4. A process of claim 2 for preparing a compound wherein R₂ is a substituted phenyl group.

5. A process of claim 1 for preparing a compound wherein R₂ is a phenyl substituted with an amino or a mono-or di-(C₁-C₄)alkylamino group.

6. A process of claim 2 for preparing a compound wherein R₂ is a phenyl substituted with an amino or a mono-or di-(C₁-C₄)alkylamino group.

7. A process of claim 1 for preparing a compound wherein R₂ is a dimethylaminophenyl group.

8. A process of claim 2 for preparing a compound wherein R₂ is a dimethylaminophenyl group.

9. A process of claim 1 for preparing a compound wherein R₁ is a methyl group and R₂ is a dimethylaminophenyl group.

10. Use of a compound of claim 1, 2, 3, 4, 5, 6, 7, or 8 for preparing a medicament for enhancing myocardial contractile force or treating heart failure.

11. A process of claim 1 wherein the thiazolone is reacted with 1.1 molar equivalents of the acid halide.

12. A process of claim 1 wherein the reaction temperature is 60°C.

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European Patent
Office

EUROPEAN SEARCH REPORT

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EP 86 11 4263

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	EP-A-0 117 082 (FUJISAWA) ----		C 07 D 277/34 C 07 D 417/06 C 07 D 417/10 A 61 K 31/425 A 61 K 31/335 A 61 K 31/415
A	GB-A-1 435 476 (ROUSSEL-UCLAF) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 277/00 C 07 D 417/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 16-12-1987	Examiner DE BUYSER I.A.F.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application I : document cited for other reasons & : member of the same patent family, corresponding document			

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